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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,869	11/29/2001	A. James Mixson	5627*6	9568

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	4

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/036,869	Mixson
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 27, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *21-40* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Nov 29, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *08/985,526* .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment were received and entered as Paper No. 7 on 11/27/02.

Claims 36-40 were added as requested.

Claims 21-40 are pending and under consideration in this Office Action.

Priority

This case is a continuation of 09/500,838, which is a continuation in part of 08/985,526, now abandoned, which is a continuation in part of 08/680,845, filed 12/5/97, now issued as US Patent 6,080,728. 08/985,526 provides no support for claims 21-35, which are directed to methods of inhibiting tumor growth through administration of RNA in a carrier that is either liposomes, cationic polymers, micelles. Additionally, the '728 patent provides no support for delivering RNA by liposomes, cationic polymers, micelles, or combinations of these carriers. For these reasons, the priority date for claims 21-35 is considered to be 2/10/00, the filing date of 09/500,838.

Objections Withdrawn

The objection to claims 21-35 over the word "lipsome" is withdrawn in view of Applicant's amendment.

Rejections Withdrawn

The rejection of claims 21-35 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendment.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 36-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,080,728 ('728). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Instant claim 36 is a method of inhibiting tumor growth in a subject bearing a tumor by administering a nucleic acid encoding at least one anti-angiogenic protein or peptide in a carrier selected from the group consisting of liposomes, cationic polymers, micelles, and a combination

thereof. Instant claim 37 requires intravenous injection, and instant claims 38-40 require a liposomal carrier, a cationic polymer carrier, or a micelle carrier, respectively.

Claim 1 of '728 is drawn to a method of inhibiting tumor growth by administering to a subject a DNA encoding an anti-angiogenic protein with a carrier which may be a liposome, a micelle, or a cationic polymer. Claim 2 requires intravenous injection, and claims 3-5 require a liposomal carrier, a cationic polymer carrier, or a micelle carrier, respectively.

Accordingly claims 1-5 of '728 teach species (methods of delivering DNA) of the claimed genus (methods of delivering nucleic acids), rendering the instant claims obvious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 21-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting tumor growth by delivery of carrier:DNA complexes, wherein the DNA encodes at least one anti-angiogenic protein or peptide, and wherein the carrier is a liposome, a cationic polymer, or a micelle, as claimed in US Patent 6,080,728, does not reasonably provide enablement for any carrier:RNA compositions for inhibiting tumor growth. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining enablement are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Nature of the invention and Breadth of the claims

3. Claims 21-35 are drawn to methods of administering RNA to a subject for the purpose of inhibiting tumor growth or providing anti-angiogenic therapy. The RNA may encode any anti-angiogenic protein or peptide, and must be in a carrier which is a liposome, a cationic polymer, or a micelle, or a combination of these carriers. The specification lists preferred carriers at page 11, lines 26-28, and discloses retroviruses as an alternative to liposomes, cationic polymers, and micelles. The specification does not contemplate the delivery of retroviruses with liposomes, a cationic polymer, or a micelle carriers. For this reason, the scope of the term "RNA" in the claimed invention excludes RNA in retroviral particles, thus the claimed invention does not encompass the delivery of retroviruses.

Claims 36-40 are drawn to methods of administering any nucleic acid encoding an anti-angiogenic protein or peptide to a subject for the purpose of inhibiting tumor growth. Thus claims 36-40 encompass methods of delivering DNA as claimed in US Patent 6,080,728, as well as methods of delivering RNAs.

State of the art, Predictability of the art, and Level of skill in the art

4. The prior art taught that tumor growth could be inhibited by systemic and direct administration of DNA expression constructs encoding anti-angiogenic proteins or peptides. See US 6,080,728, claims 1-17. The specification asserts at page 4, lines 4-8 that the level of protein expressed from mRNAs delivered to cells by liposomal vectors is similar to that obtained from delivery of DNA, citing Malone et al (Proc. Nat. Acad. Sci. USA (1989)). However, a review of Malone reveals no support for this assertion, as Malone does not report any comparison between RNA and DNA transfection. On the other hand, there are numerous reports indicating that mRNA delivery results in poorer gene expression than does DNA delivery. For example, Lu et al (1994) demonstrate that RNA/liposome transfection gave about 20-fold less expression per microgram of nucleic acid delivered than did DNA/liposome transfection. See Fig. 7 on page 251. Fisher et al (Biochem. J. (1997) 321:49-58) show that DNA/polylysine complexes gave expression efficiencies two orders of magnitude greater than the same mass of mRNA/polylysine complexes. Compare Fig. 7, panel C on page 55 with Fig. 8, panel C on page 56. Similarly, Conry et al (Cancer Research (1997) 55: 1397-1400 shows that injection of equal masses of mRNA and DNA into mouse tongue muscle in vivo resulted in nearly two orders of magnitude

greater expression for DNA over RNA. See Fig. 3 on page 1399. Furthermore, the proponents of mRNA transfection teach that this process is best suited for situations which require only transient expression of the protein of interest. See Malone (Focus (1998), page 65, column 2, lines 6-10; Dwarki et al (1993), page 654, first full paragraph, and Conry et al (1997), page 1397, column 2, lines 20-26, and Fig. 3 on page 1399. Such applications could include immunization.

The prior art teaches the delivery of mRNA *in vivo* for the purpose of stimulating an immune response against an antigen encoded by the mRNA. See e.g. Martinon et al (Eur. J. Immunol. (1993) 23: 1719-1722). However, a search of the prior art did not reveal any therapeutic immune responses induced by mRNA transfection, nor the use of mRNA transfection for any other therapeutic purpose. In fact, after the invention was filed it was noted that there are very few examples of attempted use of RNA in the field of gene therapy, due to the instability of delivered RNA, and the difficulty in working with RNA relative to plasmid DNA. See Bettinger et al (Nucl. Acids. Res. (2001) 29(18): 3882-3891, page 3882, lines 1-7. Indeed, at the time the invention was made, successful implementation of nucleic acid-mediated therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to

the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). Given that the major problems facing gene therapy in general are related to poor gene expression, and that the art teaches that gene expression from DNA transfection is generally greater and longer lasting than that obtainable from RNA transfection, even those of the highest level of skill in the biotechnological art would not have expected that the claimed invention could be operational without some improvement in the state of the art.

Guidance and Examples in the specification

5. Guidance in the specification regarding RNA transfection is essentially absent, being limited to two brief passages at page 4, lines 4-8, and page 19, lines 4-7. No specific guidance is given concerning the delivery of RNAs using the compositions and methods of the invention. For example, Applicant has failed to teach how to compensate for the fact that mRNAs are not replicated *in vivo*, and are much less stable than DNAs, whereas a single expression vector can

give rise to a large number of mRNAs over a period of days or weeks. The specification fails to address methods for increasing the stability of RNA for purposes of transfection and expression *in vivo*. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the specification entirely omits any guidance as to the amounts of specific RNAs which would be required to practice the methods, the amounts of carriers which are appropriate for each mRNA, or the appropriate modifications for increasing the stability and expression of RNA in vivo.

Amount of Experimentation required

6. Given the unpredictability of gene therapy in general, the absence of examples of therapeutic RNA delivery in the specification or the prior art, and the failure of the specification to provide any guidance whatsoever as to how to improve the stability and expression of delivered RNAs, one of skill in the art would have to perform undue experimentation in order to practice the claimed methods.

Response to Arguments

7. Applicant's arguments filed 11/27/02 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection at pages 4 and 5 of the response.

At page 4, paragraph 1, Applicant indicates that it is irrelevant that transfection of mRNA is generally results in poorer gene expression than transfection of DNA, arguing that the relevant inquiry is whether or not one skilled in the art could practice the claimed methods delivering RNA. The logic of this argument is elusive. If one cannot obtain adequate mRNA expression to perform therapy, then how can one practice the invention? The argument is unpersuasive because Applicant has not suggested any type of RNA that could be delivered other than mRNA, and the claims do not embrace the delivery of retroviral RNA for the reasons of record discussed above under *Breadth of the claims*. In the rejection it was established that

- the field of gene therapy is extremely unpredictable,

-the major barriers to success were poor gene expression, the inability to maintain gene expression, and the inability to deliver genes,

-delivered RNA is less stable in vivo than delivered DNA,

-RNA delivered in vivo is generally more poorly expressed than delivered DNA,

-those of skill in the art suggested the in vivo delivery of RNA only for purposes that require only transient gene expression, such as immunization,

-and very few attempts at RNA gene therapy had been made even after the time of filing, due to the instability of delivered RNA, and the difficulty in working with RNA relative to plasmid DNA.

It follows that if one cannot obtain adequate gene expression by delivering mRNA, then one cannot practice the invention with mRNA.

In paragraph 2 of page 4, Applicant reviews two publications from the prior art that show that mRNA can be expressed in vivo. Whether or not RNA can be expressed in vivo is not the relevant issue. The issue is whether or not one can express RNA in vivo well enough to inhibit tumor growth in a subject bearing a tumor, as discussed above. For the reasons set forth above, the specification fails to enable this process.

In paragraph three of page 4 to paragraph one of page 5 Applicant argues that the specification provides adequate guidance with regards to the dosages or RNA required to practice the instant invention. For support Applicant relies on the disclosure of Felgner (US 5,589,466) who teaches that either DNA or RNA can be delivered in vivo in amounts of 0.5 mg/kg to 5 .

mg/kg. Applicant notes that the instant specification teaches delivery of from 1 to 60 ug of RNA, alleging that this falls within the range cited by Felgner. This is unpersuasive for at least two reasons. First, Felgner clearly teaches a different range than Applicant. For a 60 kg patient, Felgner teaches delivery of 3-30 milligrams or RNA. Applicant teaches delivery of 1-60 micrograms, thus Applicant's range is 50-3000 fold lower than that of Felgner. Second, the Felgner patent contains no claims to the delivery of RNA or the treatment of tumors, rather Felgner is directed to the induction of an immune response, thus Applicant's reliance on Felgner for proof of enablement of tumor therapy is misplaced. Applicant's assertion that determination of appropriate dosages is well within the skill of the routineer is unpersuasive in light of the fact that, as established in the rejection, treatment of tumors with non retroviral RNA was not routine in the art at the time of the invention. In fact such treatments were still not routine after the time of the invention as evidenced by Bettinger et al (2001) (see above).

Finally, Applicant argues the state of the art at the time of the invention supported the use of RNA in gene therapy, relying for support on US Patent 6,135,976 issued 10/24/00. Applicant is reminded that each application is considered on its own merits, and that developments occurring after the filing date of an application are of no significance regarding what one skilled in the art believed as of that filing date. See for example, *in re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993). Applicant further argues that it is inconsistent to reject the present claims due to alleged inoperability of an entire field when the PTO has issued dozens of patents directed to gene therapy. This is unpersuasive because the rejection is not based upon the inoperability of an entire

field. When considering enablement, the state and unpredictability of the art, as well as guidance in the specification, are considerations. In highly unpredictable arts, guidance that is not available in the art must be provided by the specification. Each application is considered on its own merits. In this case, the specification fails to provide an enabling disclosure due largely to the unpredictable nature of the art and the fact that guidance in the use of RNA is limited to two brief passages at page 4, lines 4-8, and page 19, lines 4-7. These passages do not address the art recognized problems with the use of RNA in gene therapy that are discussed in the rejection, i.e. inadequate stability, delivery, and expression. For these reasons the rejection is maintained.

Summary

Claims 21-40 are under consideration.

Claims 21-40 lack adequate enablement.

Claims 36-40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,080,728 ('728).

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to

the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JEFFREY SIEW
PRIMARY EXAMINER
2/9/03